REMARKS

Upon entry of the amendments herein, claims 3-5, 12-18 and 20-22 are pending in the application. Claims 4, 5, 12-18 and 20 have been amended; claims 1, 2, 11 and 19 have been canceled; and new claims 21 and 22 have been added. No new matter has been introduced by any of the amendments herein.

This communication is submitted in response to the Advisory Action mailed January 11, 2001 and as a follow-up to March 8 and 9, 2001 telephone discussions between the Examiner and Applicants' agent. In the Advisory Action, the Examiner indicated that the claim amendments in Applicants' December 20, 2000 Amendment and Response would not be entered, but also indicated that Applicants' Response had overcome the rejections under 35 U.S.C. §112, first and second paragraphs. Since part of their response to the Examiner's §112 rejections consisted of amendments to the claims, in direct response to grounds of rejection stated by the Examiner, Applicants are uncertain as to what the Examiner considers to be the form of the claims pending prior to the present response.

For this reason, Applicants wish to make it clear that they are basing the present response on the assumption that none of the December 20, 2000 claim amendments have been entered; accordingly, all of the claim amendments in their previous response have been presented again in the present response. Applicants have further amended the claims by limitation of the claimed subject matter to the monohydrate form of the tartrate

salt, the preferred embodiment of the instant invention. Applicants maintain the right to resume prosecution of any withdrawn subject matter in a continuation application.

The claims have still further been amended in response to the Examiner's assertion in the Advisory Action that claim 18 is improperly multiply dependent. Claim 18 has been amended and new claim 22 has been added to recite the combination of limitations deleted from claim 18 upon its amendment.

In the Advisory Action, the Examiner also asserted that "claim 16 is not in the proper format." Applicants assume that this rejection is the same as that leveled in Paper No. 14, and the only reason it can be maintained is that the December 20, 2000 amendment of the claim was not entered. In Paper No. 14, the Examiner's sole ground for rejection of claim 16 under §112 was that there was insufficient antecedent basis for the language "process for the manufacture of." The Examiner indicated that replacing the phrase with "process of making" would be remedial; Applicants did this in their December 20, 2000 response and have done so again herein, and the rejection should be withdrawn.

In the Advisory Action, the Examiner also maintained the stance that the claimed invention is obvious over the disclosure of International Publication No. WO 95/11891 of Evenden et al. The Examiner provided no guidance in the Advisory Action as to any alleged flaws and/or insufficiencies in Applicants' December 20, 2000 arguments. The major points of those arguments are reiterated below, and Applicants have also provided additional arguments and showings in support of their contention that the

claimed invention is patentably distinct over the cited prior art. Full consideration of, and response to, the arguments below are respectfully requested.

From the Examiner's perspective, Applicants' previous arguments that they have selected a single base compound and a particular salt thereof from among the very large number of possibilities presented by Evenden are not persuasive. The Examiner maintains that the instant invention represents "an indiscriminate selection of 'some' among 'many'" (in seeming contradiction to the Examiner's expressed view (see below) that Evenden does not even disclose "many" possibilities in the first place). The Examiner thus maintains that the decision of In re Lemin 141 USPQ 814 is more appropriate to the present situation than either the decision of In re Ruschig 154 USPQ 118 or In re Jones USPQ2d 1941. However, the Examiner has misassessed the situation and misinterpreted Applicants' previous arguments.

In the first place, regardless of how many compounds are disclosed by Evenden, it cannot be said that the instant invention, a particular salt of a single base compound, further limited by amendment herein to a particular hydrated form of said salt, is an "indiscriminate" selection from among the possibilities. As is clear from the disclosure in the instant specification, Applicants had a particular goal, and in their selection process they discovered, without the benefit of any prior suggestion, that the tartrate salt, particularly the monohydrate form, of the disclosed base compound was superior to other salts in meeting that goal.

Furthermore, contrary to the Examiner's assertion (referring to Applicants' May 8, 2000 Response), Applicants did not state that Evenden discloses a total of 44 compounds. What Applicants stated, and what is true, is that they "have discovered a single base compound from among all of those encompassed by Evenden formula I and have further selected the tartrate salt, in particular the monohydrate, of said base compound from among the 44 salts listed in the Evenden disclosure." [Emphasis added.] An inspection of the reference cited by the Examiner reveals that formula I, in view of the variability of substituents R_1, R_2 and R_4, encompasses twenty base compounds (see, e.g., page 5, lines 1-19). Then, on page 7, lines 5-16, are listed 44 acids which can be used in the formation of pharmaceutically acceptable acid addition salts of any and all of the base compounds of formula I. Thus, the total number of possibilities disclosed by Evenden is, minimally, 20 x 44 = 880; Applicants have selected one from among this very large list of possibilities and have further limited this possibility to a particular hydrated form.

Applicants thus reiterate their assertion that, in the first place, the present invention is not an indiscriminate selection. Furthermore, not only is the selection not indiscriminate but it cannot be said to be a selection of some among many. The invocation of In re Lemin is not appropriate in this case; more appropriately, as previously asserted, In re Ruschig and/or In re Jones could be invoked. Based on his erroneous tally of 44 possibilities disclosed by Evenden, the Examiner concludes that it would have been routine to make and screen such a limited

number of compounds to determine their relative properties. However, as pointed out above and as can readily be seen from the Evenden disclosure, the number of possibilities is far greater than that appreciated by the Examiner. The making and screening of the possibilities in order to arrive at the instant invention cannot be said to be routine, nor can the selection of a single base compound, a particular salt thereof, and still further a particular hydrated form of the salt, from among all the possibilities properly be assessed as obvious.

Applicants further note that the Evenden reference was cited during examination of the International Application of which the instant application is the National Stage. In the International Search Report, the Evenden reference is listed as a "category A" reference, i.e., a "document defining the general state of the art which is not considered to be of particular relevance." This assessment was reiterated in the International Preliminary Examination Report, wherein it was stated: "No relevant prior art has been found. WO, A, 9511891 discloses the general state of the art, but is not considered to hinder a patent."

Neither the Evenden reference cited by the Examiner nor U.S. Patent No. 5,616,610 to Evenden, et al.(made of record via Applicants' Information Disclosure Statement accompanying this response), which patent issued from the U.S. counterpart application to the reference cited by the Examiner, discloses the monohydrate of the (2*R*,3*R*)-tartrate salt of (*R*)-3-*N*,*N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen. In fact, neither reference discloses

anything regarding the monohydrate, anhydrate or other forms of the tartrate or such forms of any other salt of any of the various base compounds disclosed by Evenden.

During the March telephone discussions with Applicants' agent, the Examiner expressed the view that the monohydrate, anhydrate and any other forms of the tartrate salt that may exist are structurally identical and, thus, that the Evenden disclosure constitutes a bar to patentability of the instant invention. In the first place, as set forth above, the claimed tartrate salt in any state of hydration is patentably distinct over the teaching of Evenden. Therefore, the Examiner's expressed view should not be of consequence in the determination of patentability. This notwithstanding, Applicants wish to make the following additional response to the Examiner's expressed view.

While it may be correct to assert that the chemical structures are identical among various forms of the tartrate salt, it is not correct to make the same assertion with respect to the physical structures of the various forms. For example, the crystallographic lattice structures of the monohydrate, anhydrate and other forms of the tartrate salt are quite different from each other, owing to the fact that the unit cells have different volumes resulting from different space and orientation between the molecules. These differences are readily apparent in X-ray powder diffractograms. For example, Figure 2 in the instant application clearly shows, even though the base compounds are chemically the same, that the respective hydrochloride and tartrate salts thereof are different in their

physical properties; the hydrochloride salt is hygroscopic and absorbs much greater amounts of water from the atmosphere than does the tartrate salt.

To take this one step further, Applicants wish to point out that there can be a great difference in physical properties even among forms of a particular salt differing in their levels of hydration. Figures 3 and 4 enclosed herewith show the results of comparison of the anhydrate and monohydrate forms of *R*-3-*N*,*N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate with respect to their moisture sorption and desorption curve profiles. The figures show the percent change in mass of the tested salts as a function of relative humidity (Target RH(%)).

As can be seen in Figure 3, at 20% RH the anhydrate form has increased in mass by about 1% due to water uptake. The water uptake then increases slowly up to 90% RH, at which point the uptake suddenly jumps to 3.5%. When the RH is then decreased, the anhydrate still keeps the 3.5% moisture content until 10% RH, at which point there is a sudden loss of some of the moisture absorbed during the earlier increase in RH. However, a considerable amount of the moisture is retained even when the RH is decreased to below 10%, and the original anhydrate form has been converted into a monohydrate form.

On the other hand, from Figure 4 it can be seen that the monohyrate form of the tartrate salt absorbs only a small amount of moisture with increasing percent RH; even at 90% RH, only 0.25% additional water has been absorbed. As can be seen from

Figure 4, the desorption of the monohydrate upon decreasing percent RH is the "mirror image" reverse of the absorption process. It is surprising not only that the water in the monohydrate form of the salt is so firmly bound in the crystal lattice but that the monohyrate is not converted to, for example, a dihydrate or trihydrate, with increasing percent RH.

That the anhydrate and the monohydrate forms of the tartrate salt are not the same product is further shown by X-ray powder diffraction measurements depicted in enclosed Figure 5. The location of the peaks in the X-ray powder diffractogram clearly show the difference between the monohydrate and anhydrate forms of the salt. This is the case irrespective of whether the monohydrate is prepared from a crystallization step or from the anhydrate.

In the interest of expediting prosecution of the preferred embodiment of the invention, Applicants have limited the instant claims to the tartrate monohydrate salt of the base compound; however, this action is not a concession that such is required to distinguish the instant invention from the cited Evenden disclosure. Applicants maintain that any and all forms of the tartrate salt are patentably distinct over the teaching of Evenden, and in this they are fully supported by the arguments set forth above.

Furthermore, the monohydrate form of the tartrate salt has been shown to have physical properties distinct from those of the anhydrate form and, consequently, said monohydrate must be considered to be even further distinguished from the disclosure

in the cited prior art than are tartrate salts as a whole. It is not obvious or predictable that the monohydrate form of the tartrate salt would be less hygroscopic than the anhydrate or other forms. In general, it is not obvious from the disclosure of physical properties of one form what properties another form will have.

The tendency of the anhydrate form to absorb water and to change its crystal structure is a form of physical instability. This is a disadvantage in, for example, processing the compound in wet granulation, drying and tablet compression. The consequences of this hygroscopicity cannot be precisely anticipated in any given case, since the physical properties cannot be predicted. Surprisingly, the water in the monohyrate form is firmly bound to the crystal lattice and is not released even upon heating to 70°C. This is well above commonly used process temperatures, e.g., those used during granulation and drying in the production of tablets and capsules. Further advantages of the monohydrate over the anhydrate form in this context are related to storage of final dosage forms such as tablets and capsules. The formulated monohydrate is much more resistant to cracking induced by water absorption and swelling and thus is much more suitable.

Applicants' present claim to patentability is based on the uniqueness of the monohydrate form of the tartrate salt. Said monohydrate form was never made in the prior art simply because there was no motivation to do so; this is the standard by which obviousness should be considered. Thus, in view of its novelty

and unexpected, improved properties, the claimed product is patentably distinct over the prior art.

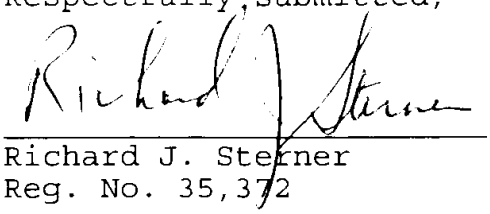
During the March telephone discussions with Applicants' agent, the Examiner also expressed the view that differences in properties such as those set forth above do not provide as compelling a case for patentabililty as do, for example, differences in utility. Applicants submit that it is inappropriate to make this distinction; they have shown that the claimed species has unexpected, superior properties, and this should be regarded as sufficient support for their assertions of patentability. The Examiner indicated that, should Applicants make their case for the patentability of the tartrate monohydrate, he would refer the case to his Supervisor for a ruling on the effectiveness of Applicants' showing. Applicants respectfully urge that the Examiner do so, in the event he himself remains unpersuaded.

The Examiner has acknowledged for the record that the claims in their present form render moot all of the prior §112 issues. In view of further amendments herein to the claims and the arguments and showings made by Applicants herein, the patentable distinction of the claimed subject matter over the cited prior art is even clearer. Reconsideration and allowance of pending claims 3-5, 12-18 and 20-22 are respectfully requested. Should any other matters require attention prior to allowance, it is requested that the Examiner contact the undersigned.

The Assistant Commissioner is hereby authorized to charge any fees which may be due any reason to Deposit Account No. 23-1703.

Dated: July 20, 2001

Respectfully submitted,



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Enclosures

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the specification:

Paragraph running from line 1 through line 8 of page 3:

The salts of the invention may be used as selective 5-HT_{1A} receptor antagonists in the treatment of CNS disorders and related medical disturbances. Examples of such disorders are depression, anxiety, obsessive-compulsive disorder (OCD), anorexia, bulimia, senile dementia, migraine, stroke, Alzheimer's disease, cognitive disorders, schizophrenia, especially [cognative] cognitive dysfunction in schizophrenia, sleep disorders, urinary incontinence, premenstrual syndrome, hypertension and pain. Examples of such medical disturbances are thermoregulatory disturbances, sexual disturbances, disturbances in the cardiovascular system and disturbances in the gastrointestinal system.

In the claims:

4. (twice amended) The salt according to claim [1] 3 in [substantially] crystalline form.

5. (twice amended) A pharmaceutical formulation containing, as active ingredient, the salt according to [any one of claims 1 to 3 or 18] claim 3 or 4 in association with a suitable diluent, excipient or an inert carrier.

12. (thrice amended) A method for [the prevention or] the treatment of [CNS] 5-hydroxytryptamine$_{1A}$-receptor-antagonist-activity-related central nervous system disorders[,] or so related thermoregulatory disturbances, sexual disturbances, disturbances in the cardiovascular system [and] or disturbances in the gastrointestinal system comprising [administration] administering, to a host in need of such [prevention or] treatment, an effective amount of the salt according to [any one of claims 1 to 3 or 18] claim 3 or 4.

13. (thrice amended) A method according to claim [11] 12 for [the prevention or] the treatment of [5-HT$_{1A}$-receptor-antagonist-activity-related CNS disorders, thermoregulatory disturbances, sexual disturbances, disturbances in the cardiovascular system and disturbances in the gastrointestinal system] obsessive-compulsive disorder, anorexia, bulimia, senile dementia, migraine, stroke, Alzheimer's disease, cognitive disorders, pre-menstrual syndrome, hypertension or pain.

14. (amended) A method according to claim 12 for the [prevention or] treatment of depression.

15. (amended) A method according to claim 12 for the [prevention or] treatment of anxiety.

16. (twice amended) A process [for the manufacture] of <u>making</u> the salt as defined in [any one of claims 1 to 3 or 18 characterized by] <u>claim 3 or 4 which comprises</u> the following consecutive steps:

i) dissolving (*R*)-3-*N*,*N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide in an appropriate solvent, optionally by heating,

ii) adding (2*R*,3*R*)-tartaric acid dissolved in an appropriate aqueous organic solvent or non-aqueous organic solvent,

iii) allowing the solution obtained to stand cold to crystallize,

iv) optionally recrystallizing in an appropriate aqueous organic solvent, if a non-aqueous organic solvent is used in step ii), to obtain the salt defined in claim [2 or 18] <u>3 or 4</u>.

17. (thrice amended) A process [for the manufacture] of <u>making</u> the salt as defined in claim [2 or 18] <u>3 or 4</u> which comprises a final step of recrystallizing (*R*)-3-*N*,*N*-dicyclobutylamino-8-

fluoro-3,4-dihydro-2*H*-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate in an appropriate aqueous organic solvent.

18. (twice amended) A process according to claim [15 or] 16, wherein the aqueous organic solvent is aqueous acetone.

20. (amended) A method according to claim 12 for [the prevention or] the treatment of urinary incontinence.